

EXHIBIT II



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Recombinant DNA Activities
National Institutes of Health, Suite 302
6000 Executive Boulevard, MSC 7010
Bethesda, Maryland 20892-7010
301-496-8838 (Phone)
301-496-8839 (Fax)

August 16, 1995

Christopher A. Maack, Ph.D.
Director, Project Management
Onyx Pharmaceuticals
3031 Research Drive, Bldg. A
Richmond, CA 94806

Dear Dr. Maack:

I have received your letter of August 11 and have had the opportunity to review it. It is my conclusion that your characterization of the attenuated adenovirus, ONYX-015, is correct. Given the definition of recombinant DNA that is contained in the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, this microorganism would be exempt since no natural or synthetic DNA segments have been added. As you pointed out correctly, wild type viruses are not subject to review; the inclusion of such agents in Appendix B is simply to provide a reference point for containment when actual recombinants of human pathogens are being studied.

Since ONYX-015 does not meet the definition of a DNA recombinant, it is exempt from review on those grounds alone, and the consolidated review process established by the NIH and the FDA for human gene transfer protocols does not apply here. In conclusion, it appears that sole review by the FDA is appropriate for this circumstance.

If you have any additional questions about this matter, please don't hesitate to contact me.

Sincerely,


Nelson A. Wivel, M.D.
Director



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Office of Recombinant DNA Activities
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October 25, 1995

Christopher A. Maack, Ph.D.
Director, Project Management
Onyx Pharmaceuticals
3031 Research Drive, Bldg. A
Richmond, CA 94806

Dear Dr. Maack:

This will acknowledge receipt of your letter of September 28. I very much appreciate seeing the additional data characterizing the attenuated adenovirus, ONYX-015. As you indicated, it would appear to be a chimeric virus created by homologous recombination in cells co-infected with adenovirus serotypes 2 and 5. As indicated previously, the definition of recombinant DNA molecules, as contained in the *NIH Guidelines*, refers to molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or molecules that result from the replication of those described above. Naturally occurring attenuations are not included in such a definition.

If you have additional questions about this matter, please don't hesitate to contact me.

Sincerely,

Nelson A. Wivel, M.D.
Director